

In the Claims:

Please amend the claims as shown:

1-27. (Cancelled)

28. (Previously Presented) A method of determining the presence of anti-Factor VIII allo-antibodies capable of degrading Factor VIII in a mammal, which comprises:

- i) isolating the plasma from a sample of blood taken from said mammal;
- ii) isolating anti-Factor VIII allo-antibodies from said plasma;
- iii) placing said anti-Factor VIII allo-antibodies in contact with Factor VIII for a period of time sufficient to permit any degradation of said Factor VIII by said anti-Factor VIII allo-antibodies; and
- iv) determining, after said period of time, whether said Factor VIII has effectively been degraded by said anti-Factor VIII allo-antibodies.

29. (Previously Presented) The method of claim 28, wherein in step ii), said anti-Factor VIII allo-antibodies are isolated from said plasma by combining them with said Factor VIII.

30. (Previously Presented) The method of claim 29, wherein said Factor VIII is coupled to a matrix.

31. (Previously Presented) The method of claim 28, wherein in step ii), said anti-Factor VIII allo-antibodies are isolated by affinity chromatography.

32. (Previously Presented) The method of claim 31, wherein in step ii), said affinity chromatography comprises the use of Factor VIII covalently coupled to a Sepharose matrix.

33. (Previously Presented) The method of claim 32, wherein said Sepharose matrix is activated with cyanogen bromide.

34. (Previously Presented) The method of claim 28, wherein in step iii), said Factor VIII is labelled with a labelling agent.

35. (Previously Presented) The method of claim 34, wherein said labelling agent is a radio-labelling agent.

36. (Previously Presented) The method of claim 35, wherein said radio-labelling agent is ¹²⁵I.

37. (Previously Presented) The method of claim 28, wherein in step iii), said Factor VIII is placed in contact with the anti-Factor VIII allo-antibodies for a period of time of between about 0.5 and about 30 hours, at a temperature of about 15 to about 40°C.

38. (Previously Presented) The method of claim 28, wherein in step iii), said Factor VIII is placed in contact with the anti-Factor VIII allo-antibodies for a period of time of about 10 hours, at a temperature of about 15 to about 40°C.

39. (Previously Presented) The method of claim 28, wherein in step iii), said Factor VIII is placed in contact with the anti-Factor VIII allo-antibodies for a period of time of between about 0.5 and about 30 hours, at a temperature of 38°C.

40. (Previously Presented) The method of claim 28, wherein in step iii), said Factor VIII is placed in contact with the anti-Factor VIII allo-antibodies for a period of time of about 10 hours, at a temperature of 38°C.

41. (Previously Presented) The method of claim 28, wherein step iv) is carried out by a determination comprising a separation technique and a visualization technique.

42. (Previously Presented) The method of claim 41, wherein said separation technique is selected from the group consisting of gel electrophoresis, and gel filtration.

43. (Previously Presented) The method of claim 42, wherein said gel electrophoresis is SDS PAGE.

44. (Previously Presented) The method of claim 42, wherein said gel filtration is fast protein liquid chromatography gel filtration.

45. (Previously Presented) The method of claim 42, wherein said visualization technique is autoradiography.

46. (Previously Presented) The method claim 28, which further comprises:

v) characterizing the site(s) in said Factor VIII molecule cleaved by said anti-Factor VIII allo-antibodies.

47. (Previously Presented) The method of claim 46, wherein said characterization is carried out by placing said Factor VIII in contact with said anti-Factor VIII allo-antibodies capable of degrading Factor VIII, separating and then sequencing the fragments of Factor VIII resulting therefrom.

48. (Previously Presented) The method of claim 47, wherein said separation is carried out using a technique such as gel electrophoresis.

49. (Previously Presented) The method of claim 48, wherein said separation is SDS PAGE.

50. (Previously Presented) The method of claim 47, wherein said sequencing is carried out using a technique such as N-terminal sequencing.

51. (Previously Presented) The method of claim 50, wherein said sequencing carried out using a technique such as N-terminal sequencing is by using an automatic protein microsequencer.

52. (Previously Presented) The method of claim 46, wherein said sequencing locates scissile bonds: Arg³⁷²-Ser³⁷³, located between the A1 and A2 domains, Tyr¹⁶⁸⁰-Asp¹⁶⁸¹, located on the N-terminus of the A3 domain, and Glu¹⁷⁹⁴-Asp¹⁷⁹⁵ located within the A3 domain of the Factor VIII molecule.

53. (Currently Amended) An amino acid sequence:

Ser Val Ala Lys Lys His Pro **(SEQ ID NO: 1)**.

54. (Currently Amended) An amino acid sequence:

Asp Glu Asp Glu Asn Gln Ser **(SEQ ID NO: 2)**.

55. (Currently Amended) An amino acid sequence:

Asp Gln Arg Gln Gly Ala Glu **(SEQ ID NO: 3)**.

56. (Previously Presented) A peptide or non-peptide analogue of an amino acid sequence of claim 53, which is capable of inhibiting any site in the Factor VIII molecule which is susceptible to being lysed by an anti-Factor VIII allo-antibody.

57. (Previously Presented) A peptide or non-peptide analogue of an amino acid sequence of claim 54, which is capable of inhibiting any site in the Factor VIII molecule which is susceptible to being lysed by an anti-Factor VIII allo-antibody.

58. (Previously Presented) A peptide or non-peptide analogue of an amino acid sequence of claim 55, which is capable of inhibiting any site in the Factor VIII molecule which is susceptible to being lysed by an anti-Factor VIII allo-antibody.

59. (Previously Presented) An anti-Factor VIII allo-antibody-catalysed Factor VIII degradation inhibitor.

60. (Previously Presented) The inhibitor of claim 59, which comprises a protease inhibitor.

61. (Previously Presented) The inhibitor of claim 60, wherein said protease inhibitor is 4-(2-aminoethyl)benzenesulphonyl fluoride hydrochloride.

62. (Previously Presented) The inhibitor of claim 59, wherein said inhibitor inhibits cleavage of the scissile bonds: Arg³⁷²-Ser³⁷³, located between the A1 domains, Tyr¹⁶⁸⁰-Asp¹⁶⁸¹, located on the N-terminus of the A3 domain, and Glu¹⁷⁹⁴-Asp¹⁷⁹⁵ located within the A3 domain of the Factor VIII molecule.

63. (Currently Amended) The inhibitor of claim 59, which comprises a peptide or non-peptide analogue of the amino acid sequence:

Ser Val Ala Lys Lys His Pro **(SEQ ID NO: 1)**.

64. (Currently Amended) The inhibitor of claim 59, which comprises a peptide or non-peptide analogue of the amino acid sequence:

Asp Glu Asp Glu Asn Gln Ser **(SEQ ID NO: 2)**.

65. (Currently Amended) The inhibitor of claim 59, which comprises a peptide or non-peptide analogue of the amino acid sequence:

Asp Gln Arg Gln Gly Ala Glu **(SEQ ID NO: 3)**.

66. (Previously Presented) A pharmaceutical composition which comprises a pharmaceutically effective amount of a pharmaceutically active ingredient selected from the group consisting of an anti-Factor VIII allo-antibody capable of degrading Factor VIII, and a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable excipient, vehicle or carrier.

67. (Previously Presented) The pharmaceutical composition of claim 66, wherein said anti-Factor VIII allo-antibody capable of degrading Factor VIII is as obtainable from the method of claim 28.

68. (Previously Presented) A method of therapeutic treatment of a mammal suffering from a pathology resulting from abnormal level of Factor VIII in the blood thereof, wherein a therapeutically effective amount of a pharmaceutically active ingredient selected from the group consisting of at least one anti-Factor VIII allo-antibody capable of degrading Factor VIII, and a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable excipient, vehicle or carrier, is administered to said mammal.

69. (Previously Presented) The method of claim 68, wherein said pathology results from the presence of an excess of Factor VIII in the blood thereof.

70. (Previously Presented) The method of claim 69, which is a therapeutic treatment of a mammal suffering from thrombosis.

71. (Previously Presented) A pharmaceutical composition which comprises a pharmaceutically effective amount of a pharmaceutically active ingredient selected from the group consisting of a Factor VIII degradation inhibitor of claim 59, and a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable excipient, vehicle or carrier.

72. (Previously Presented) The pharmaceutical composition of claim 71, which comprises a protease inhibitor.

73. (Previously Presented) The pharmaceutical composition of claim 72, wherein said protease inhibitor is 4-(2-aminoethyl)benzenesulphonyl fluoride hydrochloride.

74. (Previously Presented) The pharmaceutical composition of claim 71, wherein said inhibitor inhibits cleavage of the scissile bonds: Arg³⁷²-Ser³⁷³, located between the A1 domains, Tyr¹⁶⁸⁰-Asp¹⁶⁸¹, located on the N-terminus of the A3 domain, and Glu¹⁷⁹⁴-Asp¹⁷⁹⁵ located within the A3 domain of the Factor VIII molecule.

75. (Currently Amended) The pharmaceutical composition of claim 71, which comprises a peptide or non-peptide analogue of the amino acid sequence:

Ser Val Ala Lys Lys His Pro **(SEQ ID NO: 1)**.

76. (Currently Amended) The pharmaceutical composition of claim 71, which comprises a peptide or non-peptide analogue of the amino acid sequence:

Asp Glu Asp Glu Asn Gln Ser **(SEQ ID NO: 2)**.

77. (Currently Amended) The pharmaceutical composition of claim 71, which comprises a peptide or non-peptide analogue of the amino acid sequence:

Asp Gln Arg Gln Gly Ala Glu **(SEQ ID NO: 3)**.

78. (Previously Presented) A method of therapeutic treatment of a mammal suffering from a pathology resulting from the sub-physiological level of Factor VIII in the blood thereof, wherein a therapeutically effective amount of a pharmaceutically active ingredient selected from the group consisting of at least one Factor VIII degradation inhibitor, and a pharmaceutically acceptable salt thereof, is administered to said mammal.

79. (Previously Presented) The method of claim 78, wherein said inhibitor comprises a protease inhibitor.

80. (Previously Presented) The method of claim 79, wherein said protease inhibitor is 4-(2-aminoethyl)benzenesulphonyl fluoride hydrochloride.

81. (Previously Presented) The method of claim 78, wherein said inhibitor inhibits cleavage of the scissile bonds: Arg³⁷²-Ser³⁷³, located between the A1 domains, Tyr¹⁶⁸⁰-Asp¹⁶⁸¹,

located on the N-terminus of the A3 domain, and Glu¹⁷⁹⁴–Asp¹⁷⁹⁵ located within the A3 domain of the Factor VIII molecule.

82. (Currently Amended) The method of claim 78, which comprises a peptide or non-peptide analogue of the amino acid sequence:

Ser Val Ala Lys Lys His Pro **(SEQ ID NO: 1)**.

83. (Currently Amended) The method of claim 78, which comprises a peptide or non-peptide analogue of the amino acid sequence:

Asp Glu Asp Glu Asn Gln Ser **(SEQ ID NO: 2)**.

84. (Currently Amended) The method of claim 78, which comprises a peptide or non-peptide analogue of the amino acid sequence:

Asp Gln Arg Gln Gly Ala Glu **(SEQ ID NO: 3)**.

85. (Previously Presented) The method of claim 78, which is a method of therapeutic treatment of a mammal suffering from haemophilia A.